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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/203,768	12/02/98	WATKINS J	P-IX-2947

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EXAMINER	
HELMS, L	
ART UNIT	PAPER NUMBER
1642	15

DATE MAILED: 05/03/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/203,768	Watkins et al
Examiner	**Group Art Unit**
Larry R. Helms Ph.D.	1642

☒ Responsive to communication(s) filed on *27 Feb 2001*

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-48* is/are pending in the applicat

Of the above, claim(s) *7-46* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-6, 47, and 48* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *12*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Claims 1-48 are pending.

Claims 47 and 48 have been added.

Claims 1 and 6 have been amended.

2. Claims 7-46 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention. Applicant timely traversed the restriction (election) requirement in Paper No. 9.

3. Claims 1-6 and 47-48 are under examination.

4. The text of those sections of title 35, USC Code not included on the Office Action can be found in a prior Office Action.

5. The following Office Action contains some NEW GROUNDS of rejection.

Rejections Withdrawn

6. The rejection of claims 1-6 under 35 U.S.C. 112, second paragraph, for paragraph 6c-d of the previous Office Action, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of arguments.

Response to Arguments

7. The rejection of claims 1-6 and newly added claims 47-48 under 35 U.S.C. 112, second paragraph, for paragraph 6a-b in the previous Office Action, as being indefinite for failing to

particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained.

The response filed 2/27/00 has been carefully considered but is deemed not to be persuasive. The response states that "substantially" is clear and defined in the specification at page 16, lines 10-21. In response to this argument, one would know the amino acid sequence of SEQ ID NO:2 and 4, however, "substantially" is a relative term and not clearly defined in the specification. In addition, the response states that "similar sequences would have been identifiable based on well known methods of sequence comparison" (see page 4 of response). In response to this argument, there are numerous examples of methods for the determination of sequence comparisons and it is not clear which method would be used to determine identity or "substantially" the same. The response also states "Specifically, the canonical structure of a CDR has been defined with various nomenclatures[]the exact residue numbers which encompass a particular CDR will vary depending on the sequence and size of the CDR" (see page 5 of response). In response to this argument, it is true that three definitions are in the specification and all three are varied. Thus, one skill in the art would not know which definition to use to determine the metes and bounds of the claims because due to the variability in the definitions, one definition can encompass framework regions that are not encompassed in another definition.

8. The rejection of claims 1-6 and newly submitted claims 47-48 under 35 U.S.C. 112, first paragraph, is maintained.

The response filed 2/27/01 has been carefully considered but is deemed not to be persuasive. The response cites several references to demonstrate that fragments of an antibody that contain less than six CDRs or even a single CDR can contain binding function. In response to this argument, the art cited is not commensurate in scope with the enablement provided in the specification. The response cites Ward et al (Nature 341:544-546, 1989) for teaching a VH domain binding to lysozyme. While it is true that Ward et al did produce a VH that bound lysozyme, the VH was produced using a diverse library of VH genes and screened for binding. The claims recite at least one CDR which can bind antigen. In this context the art of Ward is not commensurate in scope because Ward et al also teach the VH domains are "sticky" (see page 546). From Ward et al it is not clear if the affinity is influenced by this "stickiness" and the other VH domains that had high affinity (those on page 546) were not taken directly from the D1.3 antibody, they were mutants of the VH. Moreover, one skilled in the art reading Ward et al would not conclude that every VH alone domain would bind antigen. As evidenced from Ward et al the Vk domain makes only a small net contribution to the energetics of binding and that was surprising since removal of a single hydrogen bond led to loss of affinity (see page 544). Thus, it seems that the binding of the VH domain of Ward et al is not universal for all VH domains alone to bind antigen. The response cites Ditzel et la (J. Immunol. 157:739-749, 1996) as evidence of single CDRs that have binding affinity for antigen. In response to this argument, the peptide comprising CDR3 of the heavy chain is a disulfide constrained peptide and not CDR3 alone. A similar response would be directed to the Williams et al (PNAS 86:5537-5541, 1989) reference

where a dimeric peptide is required for binding. The response further states that CDR shuffling is provided by Ditzel et al that demonstrates CDRs are not required to be in any order. In response to this argument, the method provided a library of both light and heavy chains and not single CDRs. The libraries were Fabs. The response cites Walsh (Nature Biotech. 18:831-833 providing evidence of antibodies having grafted CDRs. In response to this the reference shows antibody based products. With regards to Ditzel et al teaching transfer of HCDR3 to the Fab p313, Ditzel specifically teaches "the flanking sequences may be of importance for the structure of the third hyprervariable loop" (see page 742). This is important because both the LNA3 and the p313 had the denticle amino acid sequences just adjacent to the HCDR3 positions (see page 742). Thus, the specification is not enabled for any VH or VL alone or a single CDR from any of SEQ ID NO:2 or 4 as broadly claimed.

The response further states that claim 5 has been rejected for "pharmaceutical composition". The response cites antibodies that are approved for cancer therapy and the specification teaches methods of making pharmaceutical compositions (see pages 12 and 13 of response). In response to these arguments, it is immaterial that other antibodies have been approved for cancer therapy. While it may be true that the specification teaches methods to formulate antibodies, as stated in the previous Office Action, "enablement of a "pharmaceutical composition" is considered to rest on a teaching of in vivo administration for purposes consistent with the intended use disclosed in the specification. The disclosed intended use for the claimed

pharmaceutical composition is for the treatment of cancer". The specification does not enable in vivo administration of the antibody for cancer treatment.

Conclusions

9. No Claims are allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The

examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

12. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

Sheela J. Huff

SHEELA HUFF
PRIMARY EXAMINER